Attorney Docket 2000-0702/ORI

IN THE UNITED STATES OF PATENT AND TRADEMARK OFFICE

Re App:	Brian Hawtin	Art Unit:	1619
Serial No:	09/701,140	Exam:	Lauren Q Wells
Filed:	November 21, 2000		
For:	Formulation		

DECLARATION OF MARTIN CHURCH

The Commissioner of Patents and Trademarks

Washington, D.C. 20231

Sir:

I, Martin Church, hereby declare as follows:

1. That I am a citizen of the United Kingdom, and a resident of Winchester, UK, residing at 95A Hursley, Winchester, SO21 2JY, and have investigated the preparation of the present invention for its suppressive effects on histamine induced itch and flare in human skin;

2. That I am presently employed by the University of Southampton School of Medicine, Division of Infection, Inflammation and Repair, where I hold the title of Professor of Experimental Immunpharmacology, a position which I have held for 12 years.

3. That I have been engaged in the pharmacokinetics and pharmacodynamics of drugs delivered to the skin for a period of about twelve (12) years. Specifically, I have been engaged in the development and assessment of pharmaceutical compositions related to the treatment of skin-related diseases and conditions for a period of at least about 10 years. A copy of my *Curriculum vitae* is attached;

4. That in the course of these activities, I have personally become familiar with the problems encountered with transdermal transmission of pharmaceutically active drugs in topical treatments;

5. That I have become familiar with the subject matter of the references cited by the Examiner in the course of prosecution, including the following:

British Patent No 2 202 145
US Patent No 5,939,085
US Patent No US 6,143,310:

6. That the subject matter of these references do not provide the unexpected benefit of the presently claimed compositions, with the reasons being as follows:

The formulations described in the cited references, and particularly the pharmaceutical composition of Totten *et al.* have not proven to be a successful topical vehicle for the transdermal transmission of sodium cromoglycate. In investigations of the composition of the present invention, however, the sodium cromoglycate effectively suppresses itch. The combinations of the presently claimed composition, therefore, provide an unexpected level of sodium cromoglycate activity, which indicates that the presently claimed composition represents a novel and unexpected advancement in the treatment of allergic and inflammatory diseases of the skin. Specifically, the formulation described and claimed in the pending application is key to the ability of sodium cromoglycate to be effectively absorbed by the skin for direct and enhanced treatment of skin maladies. Such an effectiveness is not seen in the compositions represented in the cited references.

7. That based upon my education and experience, I am fully confident that the Totten *et al* (GB 2 202 145) reference, the Jacobs *et al.* (US 5,939,085) reference, and the Sang *et al* (US 6,143,310) reference, whether taken alone or in combination, fail to teach or suggest the unexpected beneficial results of the pharmaceutical compositions embodied in the presently pending claims;

8. That this Declaration is given for the purpose of defining and delineating distinctions present in the claimed subject matter of this application from the disclosures available in the references being relied upon by examiner, and that this Declaration is given in support of the patentability of the claims presently under consideration.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on 7th May, 2003

Martin K. Church.

CURRICULUM VITAE

MARTIN K CHURCH
University of Southampton

1. PERSONAL INFORMATION

Name: CHURCH Martin Kenyon **Title:** Professor

Date of Birth: 15 June 1942

2. PRESENT APPOINTMENT

Present post: Professor of Experimental Immunopharmacology

Department/Group: Dermatopharmacology Unit, Allergy & Inflammation Sciences Division

Faculty: Medicine, Health and Biological Sciences

Date of appointment/promotion to present post: April 1991

Previous appointments at this University immediately prior to present appointment:

Dates	Appointments
1982 - 1991	Senior Lecturer in Pharmacology, Faculty of Medicine
1976 - 1982	Lecturer in Pharmacology, Faculty of Medicine

3. PREVIOUS APPOINTMENTS

Dates	Appointments
1974 - 1976	Deputy Head of Pharmacology, Roussel Laboratories Ltd
1969 - 1974	Senior Pharmacologist, Pharmacology Research, Roussel Laboratories Ltd
1966 - 1969	Pharmacologist, Pharmacology Research, Parke Davis & Co

4. QUALIFICATIONS

Date	Title	Subject	Awarding Body
1964	BPharm (with honours)	Pharmacy	University of Wales
1966	MPharm	Pharmacology	University of Wales
1970	PhD	Pharmacology	Council for National Academic Awards
1990	DSc	Pharmacology	University of Southampton

5. **PUBLICATIONS (see attached list)**

a. Books edited = 7

b. Reviews and original manuscripts = 291

6. **MEMBERSHIP OF SOCIETIES**

British Society for Allergy and Clinical Immunology (Secretary: 1991-94; Council Member: 1994-99)
Fellow of the American Academy of Allergy, Asthma and Clinical Immunology
Member of the Collegium Internationale Allergologicum (CIA)
Member of the British Pharmacological Society
Member of the European Academy of Allergology and Clinical Immunology
Member of British Society of Investigative Dermatology

7. **MAIN RESEARCH INTERESTS**

- Mechanisms of allergic disease, particularly at the cellular level
- Mast cell biology
- *In vivo* studies of allergic and inflammatory diseases in the skin

Attorney Docket 2000-0702/ORI

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re App: Brian Hawtin Art Unit: 1619
Serial No: 09/701,140 Exam: Lauren Q Wells
Filed: November 21, 2000
For: Formulation

DECLARATION OF ALAN EDWARDS

The Commissioner of Patents and Trademarks

Washington, D.C. 20231

Sir:

I, Alan Edwards, hereby declare as follows:

1. That I am a citizen of the United Kingdom, and a resident of Newport, Isle of Wight, UK, residing at Hanover House, Brook, and involved in the clinical evaluation of the invention described in the above-identified application for United States Letters Patent;

2. That I am presently employed by Vectis Allergy Limited where I hold the title of Medical Director, a position which I have held for 7 years, it being in the business of consultancy services to the pharmaceutical industry. Prior to that I was employed by Fisons Plc from 1974 to 1995;

3. That I have been engaged in the development and assessment of pharmaceutical compositions for the treatment of skin-related diseases and conditions for a period of at least about 22 years. Specifically, I have been engaged in the development and assessment of pharmaceutical compositions comprising sodium cromoglycate and related compounds, in relation to both skin-related diseases and conditions, and other diseases and conditions for 28 years. The compositions on which I have worked include compositions for injection, oral ingestion and inhalation as well as for topical administration. A copy of my *Curriculum vitae* is attached;

4. That in the course of these activities, I have personally become familiar with the problems encountered with transdermal transmission of pharmaceutically active drugs in topical treatments;

5. That I have become familiar with the subject matter of the references cited by the examiner in the course of prosecution, including the following:

   British Patent No 2 202 145
   US Patent No 5,939,085
   US Patent No US 6,143,310;

   and, have related the substance of the presently claimed subject matter to disclosures of these references;

6. That the subject matter of these references do not provide the unexpected benefit of the presently claimed compositions, with the reasons being as follows:

   The claimed invention provides a composition comprising sodium cromoglycate for topical application to the skin. The active ingredient, sodium cromoglycate, was originally developed as an inhalation product for the treatment of asthma and its primary mode of action in this indication is thought to be the prevention of the release of inflammatory mediators from sensitised mast cells in the bronchial mucosa. As this mode of action is considered to be potentially useful in other allergic conditions, subsequent to the approval and marketing of the first anti-asthma product in the 1960's formulations have been developed for application to the nasal mucosa for the treatment of allergic rhinitis, to the conjunctiva for allergic conjunctivitis and to the gastrointestinal tract for food allergy. No product has previously been marketed for the treatment of skin conditions although there have been publications on the use of various topical applications ranging in concentration from 1% to 10% and in various carriers including water, white soft paraffin and an oil in water emulsion. Probably the main reason why these products have not been developed into marketable products has been the poor absorption of the drug through the skin. In the only study in which absorption has been measured the mean bioavailability of sodium cromoglycate in the 4% oil in water emulsion used was 0.44% of the dose applied to the skin (Ariyanayagam *et al* (1985) *Br J Dermatol* **112**, 343-348). I was involved in this study as pharmaceutical physician responsible for clinical development. Although Ariyanayagam *et al* does not provide any details of the oil in water emulsion used, from my involvement in the study I am aware that the emulsion, although developed to provide greater absorption of the drug compared to previous formulations did not succeed in this aim. There were some positive results reported in the Arianayagam trial but these were not supported by other trials using the same formulation [Pike *et al* (1988) *Eur J Pediatr;* **148**:170, Kjellman *et al*(1986) *Allergy* **11**:423-28]. Results were negative in both of these trials. Pike *et al* comment that the "lack of effect may indicate that SCG concentration at its site of action

is still inadequate in spite of improved absorption". Kjellmann *et al* comment "The parents felt disappointed that no real itch relief was obtained form use of the trial cream". We now have positive evidence from the work in Southampton (see below) that there is a direct effect on itch and I have observed this in using the new formulation on named patients.

I believe that the skin formulation of the invention is unique in that more drug is absorbed than from any previous formulation. Although the actual absorption has not yet been quantified, there is indirect evidence of good absorption:

Heat sensation. A sensation of heat in the skin is a known phenomenon of the chromone group of chemical compounds of which sodium cromoglycate is a member. The sensation was studied in most detail by Collier & Fuller [Collier JG, Fuller RW. *Br.J Clin.Pharmacol* (1983). 16 (6):639-43]. using intravenous and intra-arterial infusions of sodium cromoglycate in healthy volunteers. They reported that all 4 subjects given an intravenous infusion noticed a warm sensation which started in the perineum and in 3 spread to involve the blush areas of the chest, neck and face. When the drug was administered intra-arterially into the brachial artery a sensation of warmth was reported in 17 out of 21 occasions in 14 subjects. There was no change in skin colour and no change in skin temperature nor in blood flow. They concluded that the most likely explanation for the sensation was stimulation of sensory nerves in the skin. When I began to use different concentrations of sodium cromoglycate in the formulation of the present invention (referred to as "Altoderm") in named patients, the sensation of heat was reported in 2 of 3 subjects treated with a 7.5% concentration and 7 of 17 treated with a 4% concentration. At the higher concentration, the sensation was sufficiently uncomfortable for the treatment to be discontinued but this was only necessary in one of 4 cases at the lower concentration. This effect has not been reported in any of the published trials with other formulations and this is taken as indirect evidence that the drug is better absorbed from Altoderm. This effect was not observed in the trials reported in Ariyanayagam *et al* (1985), Pike *et al* (1988) and Kjellmann *et al* (1986) with which I was involved.

Effect on histamine challenge. The primary indication for Altoderm is atopic dermatitis. This is a common skin condition affecting 10-20% of children worldwide. Its main feature is intense pruritis (itching) and a chronic allergic inflammation. Histamine and other inflammatory mediators released from cells in the inflamed skin is thought to be the main cause for the pruritis. However conventional antihistamine drugs (H1 receptor antagonists) are only partially helpful as there are other

mediators that can cause itching. A treatment that acted on the end organ of the itching, the sensory neurones would be a distinct advance, not only in this condition but also other skin conditions in which pruritis is a primary symptom.

The chromones are highly polar agents and poorly absorbed through the skin. Recently a group at the Dermatopharmacology Unit at the University of Southampton published a study [Ahluwalia et al (2001), Br.J Pharmacol. **132 (3)**:613-16], in which they showed that the chromone, nedocromil sodium when introduced into the skin using the technique of iontophoresis, a technique that drives the drug across the skin from a chamber using a small electrical current. They showed that the drug can reduce the itch and flare induced by the intradermal injection of histamine. As the associated weal and increase in blood flow was not altered they concluded that this effect resulted from modulation of sensory neurone activation or conduction in the skin. This is a unique finding, potentially very useful in the treatment of skin conditions.

The same group have subsequently repeated the work with sodium cromoglycate (as yet unpublished). In this second experiment they applied the sodium cromoglycate both by iontophoresis and by the topical application of Altoderm. Iontophoresis, which was estimated to introduce 38.8µg of the drug over an area of 0.8cm2, resulted in a 32% reduction in itch and a 25% reduction in flare induced by intradermal histamine. One millilitre of Altoderm, the 4% concentration, massaged into an area approximately 10cm2 twice daily for 3 days before the challenge with histamine, resulted in a 28% reduction in the severity of the itch and a 29% reduction in the size of the flare. These changes were significant compared to a placebo lotion, ($p=0.024$ for itch and $p=0.001$ for flare). Concentrations of sodium cromoglycate in the Altoderm base of 1% and 2% did not have any significant effect. The results are presented in Appendix A. Iontophoresis is recognised as the optimal way of driving large ionic molecules across the skin. The similar effects on itch and flare seen whether the drug is applied using iontophoresis or application of Altoderm means that the amount of drug reaching the relevant receptors using this formulation is almost certainly greater than that seen with other formulations.

In conclusion, the present invention provides a new formulation of sodium cromoglycate for topical use. It is considered to optimise the absorption of this highly polar and lipophilic chemical through the skin. The formulation is unlike any other formulation developed for topical use on the skin. At present the only methodology known that can introduce this type of compound across the skin is iontophoresis, a technique involving an electrical current. The experiments carried out in Southampton show that the amount of drug introduced by 4% Altoderm

is in the same order as that introduced by iontophoresis. Similar conclusions can be drawn from early results in clinical usage in which an effect dependent upon high concentrations of the drug reaching sensory neurones has been observed in patients. To date Altoderm has been used in 20 named patients with varying skin conditions (See Appendix). Optimal results have been obtained in children with atopic dermatitis but adults with both atopic dermatitis and contact dermatitis have benefited. A placebo-controlled trial in children aged 2 to 12 years, with atopic dermatitis, is currently in progress. Eighty-five patients have been entered into the trial to date of whom 32 have completed 3 months treatment with Altoderm or placebo. Some children have clearly benefited and although the treatment code has not yet been broken, 24 parents have requested for treatment to be continued. This did not occur following trials with other formulations. These children have been entered into the named patient programme.

I conclude that Altoderm is a formulation that has unique properties not seen in any previous formulation. Judging from the comparison with iontophoresis, as well as with the effects seen in named patients, the transfer of drug appears to be several orders of magnitude higher than that seen with previous formulations, with potentially major clinical benefit.

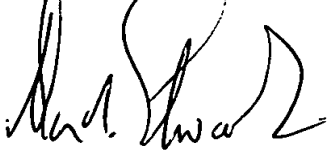
7. That based upon my education and experience, I am fully confident that the Totten *et al* (GB 2 202 145) reference, the Jacobs *et al.* (US 5,939,085) reference, and the Sang *et al* (US 6,143,310) reference, whether taken alone or in combination, fail to teach or suggest the unexpected beneficial results of the pharmaceutical compositions embodied in the presently pending claims;

8. That this Declaration is given for the purpose of defining and delineating distinctions present in the claimed subject matter of this application from the disclosures available in the references being relied upon by examiner, and that this Declaration is given in support of the patentability of the claims presently under consideration.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on 1st May, 2003

Alan M Edwards. MB BChir



Curriculum Vitae

Name: Alan Martin Edwards.

Address: Hanover House
Brook
Newport
Isle of Wight. PO30 4HG

Tel: +44 (0)1983 741116
Fax: +44 (0)1983 741119
E mail: aedwards@vectis-allergy.com

Date of birth: 11 July 1936

CITIZENSHIP: British

PRE-UNIVERSITY EDUCATION :

King's School, Worcester. 1945 - 1955

UNIVERSITY EDUCATION:

Jesus College, Cambridge. 1955 - 1958
BA 1958
MA 1963
BChir 1961
MB 1962

The London Hospital 1958-1961

POST-GRADUATE QUALIFICATIONS:

1968: Membership Royal College of General Practitioners

1977: Diploma in Pharmaceutical Medicine

PRESENT POSITION

1. Medical Director :	Vectis Allergy Limited, Hanover House, Brook, Newport, Isle of Wight. PO30 4HG UK
2. Clinical Assistant,	The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight UK :

PREVIOUS EMPLOYMENT :

Clinical.

1961-2. House Physician. Department of Paediatrics, The London Hospital, London. UK

1962. House Surgeon St. Albans City Hospital, St. Albans, UK.

1962-3. Senior House Physician. St Albans City Hospital, St. Albans, UK.

1963-8. Principal in General Practice, Hatfield, Herts. UK.

1968-74. Principal in General Practice, Reading, Berks. UK.

Pharmaceutical Industry

1974-6. Medical Adviser, Fisons A/S, Denmark

1976-7. Medical Adviser, R & D Laboratories, Fisons Pharmaceuticals, Loughborough. UK.

1977-9. Deputy Head of Medical Group, R & D Laboratories, Fisons Pharmaceuticals, Loughborough. UK.

1979-83. Medical Director, Fisons UK Operations, Loughborough. UK.

1983-8. Director of Medical Affairs, R & D Laboratories, Fisons Pharmaceuticals, Loughborough. UK.

1988-90. Regional Medical Director: UK & Northern Europe Region. Fisons Pharmaceuticals, Loughborough. UK.

1990-4. Regional Medical Director - Asia-Pacific Region, Fisons Pharmaceuticals, Loughborough. UK.

1994- 1995. Medical Adviser, Strategic Marketing Department, Fisons plc (Pharmaceutical Division), Loughborough. UK.

ADDITIONAL EXPERIENCE:

1964-1968: Clinical Assistant in Paediatrics, QE II Hospital, Welwyn Garden City Herts. UK

1968- 1974 : Clinical Assistant, General Medicine, The Battle Hospital, Reading.
Secretary, Local Medical Committee, Reading. UK

1977- 1982: Clinical Assistant, Allergy Clinic, Leicester General Hospital, Leicester. UK.

1996-2001 Clinical Assistant, Department of Medical Specialities, Southampton General Hospital, Southampton. UK

Publications:

Papers:

1. Furusho K, Nishikawa K, Sasaki S, Akasaka T, Arita M, Edwards A. The combination of nebulised sodium cromoglycate and salbutamol in the treatment of moderate-to-severe asthma in children. Pediatr Allergy Immunol 2002; 13:209-16.
2. Edwards AM. CMO (cerasomol-cis-9-cetyl Myristoleate) in the treatment of fibromyalgia: An open pilot study. J Nutr Environ Med 2001; 11:105-111.
3. Edwards AM, Howell JBL. The chromones: history, chemistry and clinical development. A tribute to the work of Dr R.E.C Altounyan. Clin Exp Allergy 2000; 30:756-74.
4. Edwards AM, Blackburn L, Christie S, Townsend S, David J. Food suplemeents in the treatment of primary fibromyalgia. J Nutr Environ Med 2000;10(3):189-99.
5. Edwards AM, Lyons J, Weinberg E, Weinberg F, Gillies JD, Reid G, Robertson CF, Robinson P, Dalton M, Van Asperen P, Wilson C, Mullineux J, Mullineux A, Sly PD, Cox M, Isles AF. Early use of inhaled nedocromil sodium in children following an acute episode of asthma. Thorax 1999;**54(4)**:308-315.
6. Sakae H, Shimoda T, Matsuo N, Matsuse H, Obase Y, Asai S, Kohno S, Edwards A. Comparison of three treatment regimens of inhaled sodium cromoglycate in the management of adult patients with severe, steroid dependent asthma. Ann Allergy Asthma Immunol 1998;80:494-498
7. Laube BL, Edwards AM, Dalby RN, Creticos PS, Norman PS. The efficacy of slow versus faster inhalation of cromolyn sodium in protecting against allergen challenge in patients with asthma. J Allergy Clin Immunol 1998; 101: 475-483.

8. Edwards AM. Oral sodium cromoglycate: its use in the management of food allergy. Clin Exp Allergy 1995; 25(Suppl.1):31-33.
9. Edwards AM. Food allergic disease. Clin Exp Allergy 1995; 25(Suppl.1):16-19.
10. Edwards AM. Sodium cromoglicate (Intal) as an anti-inflammatory agent for the treatment of chronic asthma. Clin and Exp Allergy 1994; 24:612-623.
11. Edwards AM, Stevens MT. The clinical efficacy of inhaled nedocromil sodium (Tilade) in the treatment of asthma. Eur Resp J 1993; 6: 35-41.
12. Edwards AM, Chambers A. Comparison of a lactose-free formulation of sodium cromoglycate and sodium cromoglycate plus lactose in the treatment of asthma. Curr Med Res Opin 1989; 11(5): 283-292.
13. Woodman J, Shaw RJ, Shipman J, Edwards A.M. A surveillance programme on a long-established product: Imferon (Iron Dextran BP). Pharmaceutical Medicine 1987; 1: 289-296.
14. Edwards AM, Auty RM, Clarke AJ, Orr TSC. Nedocromil sodium: A new modulator of inflammation for the treatment of asthma. J Allergy Clin Immun 1985: 75: 99.
15. Whorwell PJ, Whorwell GM, Banforth J, Jones D C, Dunn P, Edwards AM, Gent AE, Golding P, Gough K R, Hellier M D, Isaacson P, Loehrey C A, Milton-Thompson G J, Smith C L, Waldron R P, Wright R. A double blind controlled trial of the effect of sodium cromoglycate in preventing relapse in ulcerative colitis. Postgrad Med J 1981; 57(669): 436-8.
16. Buckell N A, Gould S R, Day D W, Lennard-Jones J.E, Edwards A M. Controlled trial of disodium cromoglycate in chronic persistent ulcerative colitis. Gut 1978; 19: 1140-1143.

Book Chapters.

1. Anti-asthmatic drugs. In 'Handbook of Phase I/II Clinical Drug Trials. Eds. John O'Grady, Pieter H. Joubert CRC Press Inc. 1997.
2. Anti-asthmatic drugs. in Early Phase Drug Evaluation in Man. eds. John O'Grady, Otto I. Linet. The Macmillan Press Ltd. 1990.

Conference Proceedings.

THE MAST CELL: ITS ROLE IN HEALTH AND DISEASE. Davos, Switzerland. Edited Pepys J, Edwards AM, Pitman Medical 1979.

THE ASTHMATIC CHILD IN PLAY AND SPORT. Oslo, Norway. Edited. Oseid S, Edwards AM. Pitman Medical 1983.

THE FIRST FOOD ALLERGY WORKSHOP. Chaired by Professor RRA Coombs. Medical Education Services, Oxford 1980.

THE SECOND FISONS FOOD ALLERGY WORKSHOP. Chaired by Professor RRA Coombs, Medicine, Oxford 1983.